EXHIBIT M

PDR®

56

EDITION

2002

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ISBN: 1-56363-411-2

Cont.

(S. faecalis)
lis

D RAPID BLOOD AND URINE LEVELS
ARE INDICATED, THERAPY WITH
ENICILLIN DISODIUM, SHOULD BE
PARENTERAL ADMINISTRATION FOL
E PHYSICIAN'S DISCRETION, BY ORAL

ulty testing should be performed prior to
course of therapy to detect the possible
istant organisms which may develop

ATIONS

arily contraindicated in patients who have
in allergy.

sionally fatal hypersensitivity (anaphylac-
e been reported in patients on oral penicil-
ough anaphylaxis is more frequent follow-
herapy, it has occurred in patients on oral
e reactions are more apt to occur in indi-
istory of penicillin hypersensitivity and/or a
ivity to multiple allergens.
reports of individuals with a history of pen-
itivity who have experienced severe hyper-
tions when treated with a cephalosporin.
Before initiating therapy with a penicillin,
should be made concerning previous hyper-
tions to penicillins, cephalosporins, or other
allergic reaction occurs, the drug should be
d the appropriate therapy instituted.
PHYLACTOID REACTIONS REQUIRE IM-
ERGENCY TREATMENT WITH EPINEPH-
N, INTRAVENOUS STEROIDS AND AIR-
EMENT, INCLUDING INTUBATION,
BE ADMINISTERED AS INDICATED.

NS

ith any penicillin preparation, an allergic re-
ng anaphylaxis, may occur particularly in a
individual.
of Geocillin may result in the overgrowth of
organisms. If superinfection occurs during
priate measures should be taken.
llin is primarily excreted by the kidney, pa-
ere renal impairment (creatinine clearance of
/min) will not achieve therapeutic urine lev-
llin.
th creatinine clearance of 10–20 ml/min it
ary to adjust dosage to prevent accumulation

sts: As with other penicillins, periodic as-
gan system function including renal, hepatic,
ietic systems is recommended during pro-

ns: Geocillin (carbenicillin indanyl sodium)
ay be increased and prolonged by concurrent
of probenecid.
is, Mutagenesis, Impairment of Fertility:
ong-term animal or human studies to evalu-
ic potential. Rats fed 250–1000 mg/kg/day for
eloped mild liver pathology (e.g., bile duct hy-
all dose levels, but there was no evidence of
neoplasia. Geocillin administered at daily
to 1000 mg/kg had no apparent effect on the
roductive performance of rats.
tegory B: Reproduction studies have been
dose levels of 1000 or 500 mg/kg in rats, 200
, and at 500 mg/kg in monkeys with no harm
Geocillin. There are, however, no adequate
olled studies in pregnant women. Because an-
tion studies are not always predictive of hu-
, this drug should be used during pregnancy
needed.
livery: It is not known whether the use of
mans during labor or delivery has immediate
verse effects on the fetus, prolongs the dura-
r increases the likelihood that forceps delivery
trical intervention or resuscitation of the new-
ecessary.
ers: Carbenicillin class antibiotics are ex-
although the amounts excreted are unknown;
tion should be exercised if administered to a
an.
: Since only limited clinical data is available
dren, the safety of Geocillin administration in
o has not yet been established.

EACTIONS

adverse reactions have been reported as pos-
to Geocillin administration in controlled stud-
lude 344 patients receiving Geocillin.
ast: The most frequent adverse reactions as-
Geocillin therapy are related to the gastroin-
. Nausea, bad taste, diarrhea, vomiting, flatu-

Dermatologic: Hypersensitivity reactions such as skin rash, urticaria, [illegible]pas frequently pruritus.
Hematologic: [illegible]th other penicillins, anemia, thrombocytopenia, leukopenia, neutropenia, and eosinophilia have infrequently been observed. The clinical significance of these abnormalities is not known.
Miscellaneous: Other reactions rarely reported were hyperthermia, headache, itchy eyes, vaginitis, and loose stools.
Abnormalities of Hepatic Function Tests: Mild SGOT elevations have been observed following Geocillin administration.

OVERDOSAGE

Geocillin is generally nontoxic. Geocillin when taken in excessive amounts may produce mild gastrointestinal irritation. The drug is rapidly excreted in the urine and symptoms are transitory. The usual symptoms of anaphylaxis may occur in hypersensitive individuals.
Carbenicillin blood levels achievable with Geocillin are very low, and toxic reactions as a function of overdosage should not occur systematically. The oral LD_{50} in mice is 3,600 mg/kg, in rats 2,000 mg/kg, and in dogs is in excess of 500 mg/kg. The lethal human dose is not known.
Although never reported, the possibility of accumulation of indanyl should be considered when large amounts of Geocillin are ingested. Free indole, which is a phenol derivative, may be potentially toxic. In general 8–15 grams of phenol, and presumably a similar amount of indole, are required orally before toxicity (peripheral vascular collapse) may occur. The metabolic by-products of indole are nontoxic. In patients with hepatic failure it may be possible for unmetabolized indole to accumulate.
The metabolic by-products of Geocillin, indanyl sulfate and glucuronide, as well as free carbenicillin, are dialyzable.

DOSAGE AND ADMINISTRATION

Geocillin is available as a coated tablet to be administered orally.

Usual Adult Dose

URINARY TRACT INFECTIONS	
Escherichia coli, Proteus species, and *Enterobacter*	1–2 tablets 4 times daily
Pseudomonas and *Enterococcus*	2 tablets 4 times daily
PROSTATITIS	
Escherichia coli, Proteus mirabilis, Enterobacter and *Enterococcus*	2 tablets 4 times daily

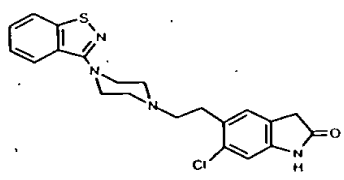
HOW SUPPLIED

Geocillin is available as film-coated tablets in bottles of 100's (NDC 0049-1430-66), and unit-dose packages of 100 (10 × 10's) (NDC 0049-1430-41). Each tablet contains carbenicillin indanyl sodium equivalent to 382 mg of carbenicillin.
Revised Sept. 1991 69-1970-00-2

GEODON™ ℞
(ziprasidone HCl)

DESCRIPTION

GEODON™ is available as GEODON Capsules (ziprasidone hydrochloride) for oral administration. Ziprasidone is an antipsychotic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1,2-benzisothiazol-3-yl) -1- piperazinyl] ethyl] -6- chloro-1, 3-dihydro -2*H*- indol-2-one. The empirical formula of $C_{21}H_{21}ClN_4OS$ (free base of ziprasidone) represents the following structural formula:



GEODON Capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate. The empirical formula is $C_{21}H_{21}ClN_4OS{\cdot}HCl{\cdot}H_2O$ and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powder.
GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. GEODON Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

CLINICAL PHARMACOLOGY

Pharmacodynamics

5HT$_{1D}$ and α_1-adrenergic receptors (K_i's of 4.8, 7.2, 0.4, 3.4, 2, and 10 nM, [illegible]ctively), and moderate affinity for the histamine H_1 [illegible] or (K_i=47 nM). Ziprasidone [illegible]tioned as an antagonist at the D_2, 5HT$_{2A}$, and 5HT$_{1D}$ [illegible]tors, and as an agonist at the 5HT$_{1A}$ receptor. Ziprasi[illegible] inhibited synaptic reuptake of serotonin and norepine[illegible]rine. No appreciable affinity was exhibited for other re[illegible]tor/binding sites tested, including the cholinergic mus[illegible]rinic receptor (IC_{50} >1 μM).
The mechanism of action of ziprasidone, as with other dr[illegible] having efficacy in schizophrenia, is unknown. However, [illegible] has been proposed that this drug's efficacy in schizophre[illegible] is mediated through a combination of dopamine type 2 (D[illegible]) and serotonin type 2 (5HT$_2$) antagonism. Antagonism at [illegible] receptors other than dopamine and 5HT$_2$ with similar re[illegible]tor affinities may explain some of the other therapeutic [illegible] side effects of ziprasidone.
Ziprasidone's antagonism of histamine H_1 receptors may [illegible] plain the somnolence observed with this drug.
Ziprasidone's antagonism of α_1-adrenergic receptors [illegible] explain the orthostatic hypotension observed with this dr[illegible]
Pharmacokinetics
Ziprasidone's activity is primarily due to the parent dr[illegible] The multiple-dose pharmacokinetics of ziprasidone [illegible] dose-proportional within the proposed clinical dose ra[illegible] and ziprasidone accumulation is predictable with mult[illegible] dosing. Elimination of ziprasidone is mainly via hepatic m[illegible] tabolism with a mean terminal half-life of about 7 hou[illegible] within the proposed clinical dose range. Steady-state [illegible] centrations are achieved within one to three days of dosi[illegible]
The mean apparent systemic clearance is 7.5 mL/min/[illegible] Ziprasidone is unlikely to interfere with the metabolism [illegible] drugs metabolized by cytochrome P450 enzymes.
Absorption: Ziprasidone is well absorbed after oral ad[illegible] istration, reaching peak plasma concentrations in 6[illegible] hours. The absolute bioavailability of a 20 mg dose [illegible] fed conditions is approximately 60%. The absorptio[illegible] ziprasidone is increased up to two-fold in the presen[illegible] food.
Distribution: Ziprasidone has a mean apparent volu[illegible] distribution of 1.5 L/kg. It is greater than 99% bo[illegible] plasma proteins, binding primarily to albumin and a[illegible] glycoprotein. The *in vitro* plasma protein bindi[illegible] ziprasidone was not altered by warfarin or propranol[illegible] highly protein-bound drugs, nor did ziprasidone alt[illegible] binding of these drugs in human plasma. Thus, the [illegible] tial for drug interactions with ziprasidone due to di[illegible] ment is minimal.
Metabolism and Elimination: Ziprasidone is exte[illegible] metabolized after oral administration with only a [illegible] amount excreted in the urine (<1%) or feces (<4%) [illegible] changed drug. Ziprasidone is primarily cleared via [illegible] metabolic routes to yield four major circulating metabol[illegible] benzisothiazole (BITP) sulphoxide, BITP-sul[illegible] ziprasidone sulphoxide, and S-methyl-dihydrozipra[illegible] Approximately 20% of the dose is excreted in the urin[illegible] approximately 66% being eliminated in the feces[illegible] changed ziprasidone represents about 44% of total [illegible] related material in serum. *In vitro* studies using [illegible] liver subcellular fractions indicate that S-methyl[illegible] drozipradone is generated in two steps. The data [illegible] that the reduction reaction is mediated by aldehyde [illegible] and the subsequent methylation is mediated by thio[illegible] yltransferase. *In vitro* studies using human li[illegible] crosomes and recombinant enzymes indicate that [illegible] is the major CYP contributing to the oxidative met[illegible] of ziprasidone. CYP1A2 may contribute to a much l[illegible] tent. Based on *in vivo* abundance of excretory met[illegible] less than one-third of ziprasidone metabolic clearance [illegible] diated by cytochrome P450 catalyzed oxidation and [illegible] imately two-thirds via reduction by aldehyde oxidas[illegible] are no known clinically relevant inhibitors or induc[illegible] dehyde oxidase.
Special Populations
Age and Gender Effects—In a multiple-dose [illegible] treatment) study involving 32 subjects, there was [illegible] ence in the pharmacokinetics of ziprasidone bet[illegible] and women or between elderly (>65 years) and yo[illegible] 45 years) subjects. Additionally, population [illegible] netic evaluation of patients in controlled trials h[illegible] no evidence of clinically significant age or gen[illegible] differences in the pharmacokinetics of ziprasid[illegible] modifications for age or gender are, therefore, [illegible] mended.
Race—No specific pharmacokinetic study was [illegible] investigate the effects of race. Population phar[illegible] evaluation has revealed no evidence of clinically [illegible] race-related differences in the pharmaco[illegible] ziprasidone. Dosage modifications for race ar[illegible] not recommended.
Smoking—Based on *in vitro* studies utilizing [illegible] enzymes, ziprasidone is not a substrate for C[illegible] ing should therefore not have an effect on th[illegible] netics of ziprasidone. Consistent with these [illegible] population pharmacokinetic evaluation has [illegible] any significant pharmacokinetic differences [illegible] ers and nonsmokers.
Renal Impairment—Because ziprasidone is [illegible] lized, with less than 1% of the drug excreted [illegible] nal impairment alone is unlikely to have a [illegible] the pharmacokinetics of ziprasidone. The [illegible] of ziprasidone following 8 days of 20 mg